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| EXAMINER | |
|---|---|
| SZPERKA, MICHAEL EDWARD | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 08/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/644,434 | KRUEGER ET AL. | |
| | Examiner | Art Unit | |
| | Michael Szperka | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-16 are pending in the instant application.

Applicant's IDS received July 6, 2004 is acknowledged and has been considered.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method determining the risk of developing thrombocytopenia as a result of GPIIb-IIIa receptor antagonist treatment when the platelet CD32 phenotype is known, does not reasonably provide enablement for a general assay method for determining the risk of developing thrombocytopenia as a result of GPIIb-IIIa receptor antagonist treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has claimed an assay method to determine the risk or presence of developing thrombocytopenia as a result of GPIIb-IIIa receptor antagonist therapy. A preferred embodiment of this method adds in steps of determining the allele of CD32 expressed on the platelets used in the assay. It is well known in the art that a

polymorphism in CD32 significantly influences the activation of platelets in assays designed to measure heparin induced thrombocytopenia (Brandt et al., reference C4 on the IDS received July 6, 2004, see entire document, particularly the abstract and the first paragraph of the discussion on page 1569). Assays that do not account for the polymorphism in CD32 suffer from high false negative results, such incorrect results being obtained potentially up to 25% of the time due to the frequency of the unresponsive CD32 phenotype in the population (see particularly the last full paragraph of the right column of page 1569). This is a serious problem since the doctors in charge of the patient will not know the cause of the thrombocytopenia and may either continue or initiate a new treatment therapy that exacerbates the patient's condition. The HIT assay taught by Brandt et al. measures the effect of anti-heparin antibodies on platelet activation, and the anti-GPIIb-IIIa receptor antagonist antibodies found in the patient samples of the instant claims are also detected via their ability to influence platelet activation. As such, an assay for determining the risk or presence of developing thrombocytopenia as a result of GPIIb-IIIa receptor antagonist therapy as taught by the instant methods will also suffer from a high rate of false negatives unless the CD32 phenotype is known and assay steps are performed to account for the differences in platelet activation caused by the different CD32 phenotypes present in the general population. While some currently recited limitations determine the CD32 phenotype, there do not appear to be any method steps that indicate the significance of this determination, or how such information is to be used to calibrate the assay so that a

correct diagnosis of the presence or risk of developing thrombocytopenia as a result of GPIIb-IIIa receptor antagonist therapy.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 2, 4-7 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. (of record as reference C4 on the IDS received July 6, 2004, see entire document) in view of Billheimer et al. (US Patent No. 6,623,981, see entire document).

Brandt et al. teach that thrombocytopenia can occur in patients treated with heparin (see entire document, particularly the abstract). This phenomenon is known as heparin induced thrombocytopenia (HIT) and is characterized by the presence of antibodies in the patient that activate normal donor platelets *in vitro* in the presence of heparin. Platelet activation by these antibodies occurs through CD32 (FcγRII), with the magnitude of platelet activation being dependent upon the allelic form of CD32 that is expressed by the platelets (see particularly the last sentence of the abstract and the last two paragraphs of the Introduction). Heparin specific antibodies are bound to platelets via CD32, and in the presence of heparin these receptors are crosslinked, leading to activation of the platelets.

Brandt et al. then disclose an assay method that tests for risk of thrombocytopenia comprising the steps of a) obtaining blood from a patient, b) separating the blood into platelet-rich plasma (PRP) and platelet-poor plasma (PPP), c) adding heparin to the patient samples, d) adding a submaximal concentration of the platelet agonist ADP, e) measuring platelet aggregation, and f) confirming a diagnosis of HIT when the difference in aggregation between patient and normal PPP in the presence of heparin was greater than or equal to 20% (see particularly the Materials and methods subsections *Preparation of Platelet-Rich Plasma for Aggregometry* and *Platelet Aggregometry* on the left column of page 1565). Note that the specification defines a submaximal concentration of ADP as being about 0.05 μM to about 5.0 μM (see particularly lines 15-17 of page 8), and the concentrations of ADP used by Brandt et al. fall within this range. Brandt et al. also perform this assay in the presence of

antibodies that specifically bind CD32, one of which (41H16) binds to CD32 that bears an arginine at position 131 but does not bind CD32 bearing a histidine at position 131 (see particularly the Materials and Methods sections *Effect of Monoclonal Antibodies on Platelet Aggregation* and *Characterization of Platelet FcγRIIa Phenotype* on page 1565). They observed that platelet aggregation induced by plasma from HIT patients in the presence of heparin could be could be inhibited in the presence of one anti-CD32 antibody (see particularly the end of the first full paragraph of the left column of page 1567), and that co-stimulation with a subaggregating concentration of ADP and HIT plasma caused aggregation of His/His131 platelets (see particularly the last sentence of the second full paragraph of the left column of page 1570, Figure 5, and Table 2). Platelets from either patients or donors can be used in methods that confirm the diagnosis of HIT, but the phenotype of the platelets used in the aggregation assay must be known beforehand since the Arg/His131 polymorphism critically influences the measured in vitro aggregation response and failure to account for this polymorphism can lead to a high rate of false negative results (see particularly the first paragraph of the discussion and the beginning of the last full paragraph of the right column of page 1569).

The teachings of Brandt et al. differ from the claimed invention in that they do not disclose that their assay method can be used to detect the presence of antibodies specific for other drugs, such as GPIIb-IIIa antagonists, that lead to the development of thrombocytopenia.

Billheimer et al. teach that drug-dependent antibodies (DDABs) develop in patients receiving treatment with GPIIb-IIIa antagonists, and that these antibodies lead to the development of thrombocytopenia in said patients (see entire document, particularly the abstract, lines 9-40 of column 1, and lines 27-34 of column 3). They further teach that the general phenomenon of drug-dependent thrombocytopenia is well known, with the best known clinical example being heparin-induced thrombocytopenia (HIT) (see particularly from line 41 of column 2 to line 6 of column 3).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the methods taught by Brandt et al. to determine the risk of developing thrombocytopenia as a result of GPIIb-IIIa receptor antagonist therapy. The necessary modifications are changing the patient population assayed and using a GPIIb-IIIa antagonist rather than heparin in the methods of Brandt et al. Motivation to make such substitutions comes from the teachings of both Brandt et al. and Billheimer et al. that patients suffering from HIT contain DDABs specific for heparin, and the teachings of Billheimer et al. that DDABs can be detected in thrombocytopenic patients receiving many different drugs, including the GPIIb-IIIa receptor antagonist abciximab (see particularly lines 29-40 of column 2 of Billheimer et al.). As such, the presence of DDABs in a patient is diagnostic for the development of drug induced thrombocytopenia, and many different drugs, such as heparin and the GPIIb-IIIa receptor antagonist abciximab, are known to induce both DDABs and thrombocytopenia. The methods of Brandt et al. indirectly identify the presence of DDABs to heparin, and as such a person of ordinary skill in the art would have a

reasonable expectation of success in modifying the methods of Brandt et al. to detect GPIIb-IIIa receptor antagonist induced thrombocytopenia. This is because the expected mechanism by which DDABs activate platelets in HIT (which is the basis of the HIT diagnostic assay method taught by Brandt et al.) and in GPIIb-IIIa receptor antagonist induced thrombocytopenia are similar.

6. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. (of record as reference C4 on the IDS received July 6, 2004, see entire document) in view of Billheimer et al. (US Patent No. 6,623,981, see entire document) as applied to claim 1 above, and further in view of Janeway et al. (Immunobiology, Third edition, page 2:12).

The teachings of Brandt et al. and Billheimer et al. have been discussed above. The instant method differs from that recited in claim 1 in that it now include the limitation that platelets be obtained from an ABO-compatible donor, and neither Brandt et al. nor Billheimer et al. appear to discuss the relevance of using ABO matched serum and platelets.

Janeway et al. teaches that the ABO blood groups are caused by the presence of differing carbohydrate structures on the surfaces of cells that are recognized by antibodies. A person of one blood group, for example "A", will have antibodies that bind to the carbohydrate structure in a "B" individual but will not have antibodies that react to the "A" carbohydrate structure. The presence of such antibodies leads to aggregation

when cells of one blood type are mixed with a sample containing antibodies of another blood type (see Figure 2.9 on page 2:12 of Janeway et al.). This aggregation has nothing to do with the presence or risk of developing thrombocytopenia. If ABO matching was not performed, no meaningful data could be obtained because the platelets would aggregate/agglutinate due to the presence of anti-A or anti-B antibodies and not due to the activation of platelets.

Therefore, a person of ordinary skill in the art would have been motivated to take the obvious step of ABO matching patient and donor samples in order to prevent the occurrence of aggregation/agglutination reactions that are not related to platelet activation caused by DDABs.

7. Claims 1 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. (of record as reference C4 on the IDS received July 6, 2004, see entire document) in view of Billheimer et al. (US Patent No. 6,623,981, see entire document) as applied to claim 1 above, and further in view of Tomer (US Patent No. 5,763,201, of record as reference A3 on the IDS received July 6, 2004, see entire document).

The teachings of Brandt et al. and Billheimer et al. have been discussed above in relation to claim 1. The instant methods differ from the method of claim 1 in that flow cytometric techniques are now recited as being used to determine platelet activation.

Tomer teaches flow cytometric techniques that measure platelet activation (see entire document, particularly the abstract). These techniques offer the advantages of ease, rapidity, and reliability when assaying platelet activation as compared to other methods (see particularly lines 23-42 of column 3). A specific reagent used by Tomer is annexin V, a protein known to bind to phosphatidylserine expressed on the surface of activated platelets (see particularly lines 56-59 of column 7 and lines 45-59 of column 8).

Therefore, a person or ordinary skill in the art at the time the invention was made would have been motivated to use a flow cytometry assay to measure platelet activation, such as by detecting annexin V binding to phosphatidylserine, as taught by Tomer because such an assay would allow for an easy, rapid and accurate determination of platelet activation.

8. Claims 1 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brandt et al. (of record as reference C4 on the IDS received July 6, 2004, see entire document) in view of Billheimer et al. (US Patent No. 6,623,981, see entire document) in view of Tomer (US Patent No. 5,763,201, of record as reference A3 on the IDS received July 6, 2004, see entire document) as applied to claim 1 above, and further in view of Holmes et al. (in Current Protocols in Immunology, (2001) 5.3.1-5.3.24, see entire document).

The teachings of Brandt et al. Billheimer et al. and Tomer have been discussed above in reference to claim 1. These teachings differ from the instant recited methods

in that the specific timing of the addition of the reagent used to detect platelet activation is not disclosed.

Holmes et al. teach that alterations in the timing and concentration at which various reagents are added in a flow cytometry method are routinely performed when optimizing the assay protocol (see particularly the Commentary section from page 5.3.14 to 5.3.22, most particularly the left column of page 5.3.18).

Therefore, a person of ordinary skill in the art would have been motivated to change the time when a platelet detection reagent was added to the flow cytometry assay based upon the teachings of Holmes et al. that alterations in when reagents are added as part of an assay method are routinely performed when optimizing a protocol. It is further noted that upon reviewing the specification it does not appear that the timing of the addition of the platelet activation reagent as recited by Applicant is critical in performing the claimed assay. As such it would have been prima facie obvious to add the reagent to detect platelet activation prior to the addition of other reagents, especially in the absence of evidence to the contrary.

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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